

The opinion in support of the decision being entered today was *not* written for publication and is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* JACQUES DUMAS, UDAY KHIRE, TIMOTHY B. LOWINGER,  
BERNARD RIEDL, WILLIAM J. SCOTT, ROGER A. SMITH,  
JILL E. WOOD, HOLIA HATOUM-MOKDAD, JEFFREY JOHNSON,  
ANIKO REDMAN, and ROBERT SIBLEY

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Appeal 2006-3205  
Application 09/472,232  
Technology Center 1600

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Decided: April 24, 2007

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Before DEMETRA J. MILLS, LORA M. GREEN, and NANCY J. LINCK,  
*Administrative Patent Judges.*

LINCK, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a 35 U.S.C. § 134 appeal in the above-referenced case.<sup>1</sup> The claimed invention “relates to the use of a group of aryl ureas in treating raf

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<sup>1</sup> The application was filed December 27, 1999. The real party in interest is Bayer Pharmaceuticals Corporation.

mediated diseases, and pharmaceutical compositions for use in such therapy.” Specification (“Spec.”) at 1. The Examiner has rejected claims 15-16, 18-23, 26-29, and 38 under 35 U.S.C. § 112, first paragraph, for lack of enablement; and claims 1, 2, 4-6, 9-10, 15-16, 18-24, 26-31, 38, and 40 under § 103(a) over U.S. 6,080,763 (“Regan”).<sup>2</sup> We have jurisdiction under 35 U.S.C. § 6(b).

We affirm both grounds of rejection.

### STATEMENT OF THE CASE

The title of Appellants’ application is: “Inhibition of RAF Kinase Using Aryl and Heteroaryl Substituted Heterocyclic Ureas.” Spec. at 1. The claimed subject matter is reflected in representative claims 15, 26, and 40, reproduced in relevant part below:<sup>3</sup>

15. A method for the treatment of disease mediated by raf kinase, comprising administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof to a host in need thereof:



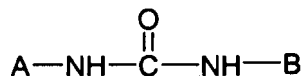
....

26. A method for treating a solid cancer, melanoma or adenoma, comprising administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof to a host in need thereof:

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<sup>2</sup> Regan was filed Oct. 29, 1998 and issued June 27, 2000.

<sup>3</sup> These claims are reproduced in their entirety in the Appendix to this opinion.



I

....

40. A compound which is

....

N-(1-(3-nitrophenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-phenoxyphenyl)urea

....

According to the specification:

It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway . . . leads to the reversion of transformed cells to the normal growth phenotype . . . . [Researchers] have further indicated that inhibition of raf expression by antisense RNA blocks cell proliferation in membrane-associated oncogenes. Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types . . . .

....

The present invention provides compounds which are inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of p21<sup>ras</sup>, the instant inhibitors are useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated . . . . In particular, the compounds are useful in the treatment of human or animal . . . cancer. . . . [Spec. 1-2.]

#### ISSUES ON APPEAL

35 U.S.C. § 112, ¶ 1 Issue

The Examiner contends Appellants' method claims, while enabled for the treatment of colon cancer, are not enabled for the treatment of "all other diseases of the instant claims." Answer 3. He further contends "no compound has ever been found to treat cancers of all types generally." *Id.*

According to the Examiner,

the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. . . . Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. . . . Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers and/or diseases mediated by raf kinase in general. [*Id.* at 4.]

After applying the *Wands* factors to the facts of the case, the Examiner concludes: "In view of the breadth of the claim[s], the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims." Answer 6.

Appellants contend the state of the art supports the breadth of their claims, relying on a number of publications as representative of the state of the art. According to Appellants:

These publications demonstrate the inhibition of raf kinase was correlated with the inhibition of the growth of a variety of tumor types . . . . Treatment approaches dependent on the inhibition of raf signaling were developed by the mid-late 1990's and a number of research groups disclosed assays for measuring the ability of compounds to inhibit raf activity, consistent with the present application.

....

These disclosures demonstrate the state of the art was not limiting with respect to the types of cancerous cell growth treated where raf plays a role. [Br. 3-5.]

Appellants further contend:

Appellants do not claim treating "all types of cancers" and do not claim the compounds disclosed are "silver bullets." The diseases to be treated are mediated by raf kinase, which is consistent with the activity demonstrated by the assay disclosed in the application. . . . No evidence has been presented that the assay disclosed in the application is ineffective for predicting the pharmaceutical use of the instant compounds and supporting the method of treatment claims. [Reply 2.]

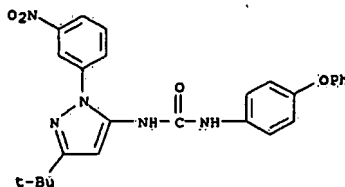
In view of these conflicting positions, we frame the § 112 issue:

Would Appellants' specification, disclosing an *in vitro* and an *in vivo* assay for inhibiting colon cancer, have enabled any person skilled in the relevant art to use the full scope of their claimed genus for the treatment of any "disease mediated by raf kinase," or alternatively, any "solid cancer, melanoma or adenoma," including those not mediated by raf kinase?

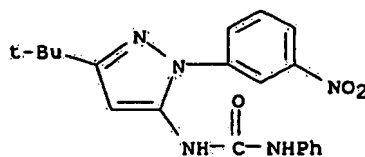
35 U.S.C. § 103(a) Issue

The Examiner contends:

A compound according to claim 40 has the following structure (third compound):



The reference disclosed compounds include the following species (see Table 1, Ex. No. 34):



As can be seen from the above two structures, the compound according to claim 40 differs from the reference disclosed compound by having a -OPh substituent on the phenyl group. The reference however, teaches the equivalency of unsubstituted phenyl and phenyl substituted with substituents selected from . . . phenoxy (i.e., -OPh), etc. and therefore, provides sufficient motivation to one skilled in the art to make the instantly claimed compound[] . . . , in the expectation that compounds similar in structure will have similar properties. Thus, the reference teaches structurally analogous compounds which are disclosed to be useful as therapeutic agents. [Answer 16-17.]

Appellants respond:

The Examiner identifies . . . example[] 34 of Regan et al. and alleges it would be a simple substitution of one substituent to obtain a compound of the present invention. However, by starting with compound[] 34 and ignoring the other examples, the examiner has preselected values for [Regan's] "HET", "Y" and "X" using, in hindsight, Appellants' application as a guide. There is no motivation or direction to pair the selections for "HET", "X" and "Y" with the specific selections necessary from the broad definition of R<sub>5</sub> to arrive at compounds of this invention. [Reply 5.]

In view of the above contentions, we frame the § 103(a) issue:

Without the use of hindsight, would it have been obvious to the skilled artisan to substitute a phenoxy group on the terminal phenyl of Regan's Example No. 34, thereby obtaining a compound expressly recited in Appellants' claim 40?

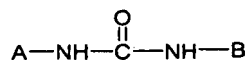
## FINDINGS OF FACT

### *Claim Interpretation*

1. Method claim 15 encompasses the treatment of all diseases “mediated by raf kinase.”
2. Method claim 26 encompasses the treatment of all solid cancers, melanomas and adenomas and is not limited by the language “mediated by raf kinase” and therefore includes the recited cancers whether or not mediated by raf kinase.

### *§112 Support for the Claimed Invention in the Specification*

3. The specification discloses and claims a relatively large genus of compounds with a urea backbone, defined generally by the “structure”



wherein A is a heteroaryl moiety, and B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety. *See, e.g.*, Spec. at 2 & claim 15. According to the specification, these compounds are “inhibitors of the enzyme raf kinase” and thus “are useful in pharmaceutical compositions . . . where inhibition of the raf kinase pathway is indicated.” Spec. at 2.

4. Thirty-two compounds within the claimed genus have been synthesized. Spec. at 29-33.
5. The specification discloses an *in vitro* raf kinase assay using these 32 exemplified compounds. Spec. at 34. This assay evidences inhibition of raf kinase by the exemplified compounds, yielding IC<sub>50</sub>s of between 10 nM and 10 μM. *Id.*
6. The specification also discloses an *in vitro* cellular growth assay, in which “human tumor cell lines, including . . . HCT116 and DLD-1 [colon

cancer cell lines], containing mutated K-ras genes are used in standard proliferation assays.” Spec. at 34. Unidentified compounds “are titrated’ and proliferation “is monitored” *id.*, but no proliferation data is disclosed. At most, these assays evidence the inhibition of colon cancer cells by some unidentified compounds within Formula I.

7. The specification summarizes an *in vivo* assay that “can be performed” to determine the “inhibitory effect of the compounds on tumors,” by injecting human colon adenocarcinoma cells into mice and then dosing the mice for 14 days, again with an unidentified compound. *Id.* This assay would have suggested to the skilled artisan how to perform an *in vivo* assay in mice for the growth of colon cancer.

8. The specification does not disclose any art-recognized assays or tests that would have been predictive of success for the pharmaceutical uses of claimed in claims 15 and 26. *See Answer 5.*

9. “[N]o *in vivo* test procedures are provided for the compounds commensurate in scope” with the claims “and there is no disclosure regarding how the *in vitro* results correlate to *in vivo* tests.” Answer 5.

10. “*In vivo* test procedures are provided for the cancers of the colon in mice (see page 35), however, there is no demonstrated correlation that the tests and results apply to all of the disorders embraced by the instant claims.” *Id.*

§ 112 Support in the Prior Art

11. The following references are relied upon to show the state of the art at the time the application was filed: Daum et al. (“Daum”), 19 *Trends Biochem. Sci.* 474-80 (1994); Fridman et al. (“Fridman”), 269 *J. Biol. Chem.* 30105-08 (1994); Kolch et al. (“Kolch”), 349 *Nature* 426-28 (1991); Monia



et al. (“Monia”), 2 *Nat. Med.* 668-75 (1996); WO 97/36587 (“WO ‘587”) (published 9 October 1997); WO 98/22103 (“WO ‘103”) (published 28 May 1998); and 1 CECIL TEXTBOOK OF MEDICINE (“CECIL”) 1004-10 (20<sup>th</sup> ed. 1996).

12. Daum and Fridman studied the inhibition of ras “by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase or dominant negative MEK” and “reversion of transformed cells to normal growth phenotype.” Spec. 1.

13. Fridman hypothesizes that “a highly specific anti-Ras chemical drug . . . that functionally mimics either Raf75 or NF78 and can be delivered efficiently into the cytoplasm . . . would be *potentially* useful for the treatment of Ras-associated cancers.” Fridman at 30108 (emphasis added).

14. Neither Daum nor Fridman studied the treatment of any type cancer with a “chemical drug,” such as those claimed by Appellants, or even suggested a possible structure for such a drug. *See* Daum & Fridman, *passim*.

15. Kolch’s research suggests that “inhibition of raf expression by antisense RNA blocks cell proliferation in membrane-associated oncogenes” (Spec. 1-2).

16. Similarly Monia “inhibit[s] raf kinase (by antisense oligodeoxynucleotides)” (Spec. at 2), and states “novel therapies directed against *raf* kinases *may* prove useful in the treatment of *ras*-dependent tumors.” Monia, at 668 (emphasis added). Monia notes “the emergence of novel therapies that specifically reverse the oncogenic effect of these gene products has generally been slow.” *Id.*

17. Monia, Kolch, Daum, and Fridman invite further research into the treatment of cancer through inhibition of raf kinase.

18. Monia, Kolch, Daum, and Fridman do not provide enabling support for the broad scope of Appellants' method claims, particularly given the claim language "disease mediated by raf kinase" (claim 15) and "solid cancer, melanoma or adenoma" without limitation to raf kinase mediation (claim 26). *See Answer 8.*

19. WO '103 summarizes the prior art and concludes "raf is both a direct and major effector of ras function and is expected to have antitumor activity in at least a proportion of human tumors." WO '103 suggests a list of "[s]pecific cancers of interest" to study and suggests raf inhibitors "*may* also be useful' in treating diseases other than cancer "that *may* be associated with signal transduction pathways operating through Ras." WO '103, at 2 (emphasis added).

20. WO '587, in discussing the work of others, states: "Antisense constructs which reduce cellular levels of c-Raf . . . inhibit the growth of oncogene-transformed rodent fibroblasts in soft agar . . . . Since inhibition of growth in soft agar is highly predictive of tumor responsiveness in whole animals, these studies *suggest* that the antagonism of Raf is an effective means by which to treat cancers in which Raf plays a role." WO '587, at 1 (emphasis added).

21. These discussions in the background sections of WO '103 and WO '587 set the stage for further research rather than providing enabling disclosure commensurate in scope with Appellants' method claims.

22. "All cancers invade or metastasize, but each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study." CECIL 1004.

23. "[C]linical and laboratory observations have provided a reasonable framework" but this "framework must be used with caution . . . because it is certain that the intrinsic factors that control tumor growth and propagation are far more complex, episodic, and heterogeneous than we know, even with a single tumor mass." CECIL 1004.

24. "At its best, oncology has pointed the way to an understanding of the biologic variability of cancer and the success that is possible with a coordinated multimodal approach to therapy." CECIL 1005.

25. "The use of scientific methods in oncology is only in its adolescence, and definitive treatment has been established for only a small proportion of circumstances and types of cancers that can arise." CECIL 1006.

26. The state of the art, as reflected in the prior art cited above, does not support Appellants' position that only routine experimentation would be necessary to practice the full scope of claims 15 and 26.

*Other Findings Relating to Enablement*

27. The evidence of record does not disclose any known compounds of similar structure, which have been demonstrated to treat all diseases mediated by raf kinase, or all solid tumors, melanomas and adenomas. *See Answer 5.*

28. "Pharmacological activity in general is a very unpredictable area." *Answer 5.*

*The Prior Art and the Graham Factors*

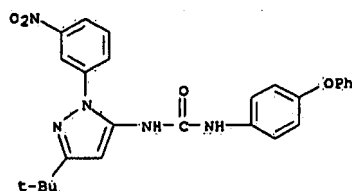
29. Regan discloses aromatic heterocyclic compounds, including aryl and heteroaryl substituted heterocyclic ureas, for “treating diseases and pathological conditions involving inflammation.” Regan, col. 1, ll. 11-15 & cols. 32-38.

30. Regan’s genus “embraces” Appellants’ claimed genus. Answer 6; *see also* Br. 10.

31. Regan also discloses a number of species, including the following compound (TABLE 1, Ex. No. 34):



32. This compound differs from one of Appellants’ claimed compounds, N-(1-(3-nitrophenyl)-3-tert-butyl-5-pyrazolyl)-N’-(4-phenoxyphenyl)urea, in that the phenyl (Ph) is substituted with phenoxy (OPh):



Claim 40 (third recited compound).

33. Regan “teaches the equivalency of unsubstituted phenyl and phenyl substituted with . . . phenoxy (i.e., -OPh).” Answer 17. *See also*, e.g., Regan, col. 18, ll. 43-55.

34. Thus, a single substitution in Regan’s Example 34 would have resulted in at least one of Appellants’ claimed compounds.

35. Such a substitution would not require preselecting “HET,” “X,” or “Y,” as Regan made this “selection” in formulating the species of Example 34.

36. One skilled in the relevant art would have reasonably expected that Appellants’ N-(1-(3-nitrophenyl)-3-tert-butyl-5-pyrazolyl)-N’-(4-phenoxyphenyl)urea, a compound falling within Regan’s “ultimately preferred” genus, would be useful as a therapeutic agent. Regan, col. 16, l. 66 to col. 19, l. 8. *See also* Answer 17.

37. Regan’s teaching of an analogous compound in Example 34, useful as a pharmaceutical for treating chronic inflammatory diseases, and the equivalence of closely related compounds, i.e., ones differing in only one position, would have motivated the skilled artisan to modify Regan’s analogous compound in Example 34, thereby obtaining N-(1-(3-nitrophenyl)-3-tert-butyl-5-pyrazolyl)-N’-(4-phenoxyphenyl)urea, a compound recited in claim 40. *See* Answer 16-17.

38. Appellants have not provided any evidence that their claimed compounds would have unexpected results compared to those disclosed by Regan. *See Br. passim.*

## PRINCIPLES OF LAW

### 35 U.S.C. § 112, ¶ 1: Enablement

Enablement is a question of law, based on underlying findings of fact. *See, e.g., In re Wands*, 858 F.2d 731, 735, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). “[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without ‘undue experimentation.’” *In re Wright*, 999 F.2d 1557, 1561, 27

USPQ2d 1510, 1513 (Fed. Cir. 1993) (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Thus, “there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.” *In re Vaeck*, 947 F.2d 488, 496 & n. 23, 20 USPQ2d 1438, 1445 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372, 52 USPQ2d 1129, 1138.

Factors to be considered in determining whether a disclosure would require undue experimentation . . . the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [*Id.* at 737, 8 USPQ2d at 1404.]

“Patent protection is granted in return for an enabling disclosure . . . , not for vague intimations of general ideas that may or may not be workable.” *Genentech*, 108 F.3d at 1365, 42 USPQ2d at 1005. “Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, *reasonable detail* must be provided in order to enable members of the public [skilled in the art] to understand and carry out the invention.” *Id.*, 42 USPQ2d at 1005 (emphasis added).

35 U.S.C. § 103(a)

“While the ultimate conclusion of obviousness is for the court to decide as a matter of law, several factual inquiries underlie this determination. These inquiries include the scope and content of the prior art, the level of ordinary skill in the field of the invention, [and] the differences

between the claimed invention and the prior art.” *SIBIA Neurosciences, Inc. v. Cadus Pharmaceutical Corp.*, 225 F.3d 1349, 1355, 55 USPQ2d 1927, 1930 (Fed. Cir. 2000) (internal citations omitted).

“In appropriate circumstances, a single prior art reference can render a claim obvious. However, there must be a showing of a suggestion or motivation to modify the teachings of that reference to the claimed invention in order to support the obviousness conclusion. This suggestion or motivation may be derived from the prior art reference itself.” *Id.* at 1356, 55 USPQ2d at 1931 (internal citations omitted). “Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness.” *Id.*, 55 USPQ2d at 1931.

## DISCUSSION

35 U.S.C. § 112, ¶ 1

Based on the Examiner’s findings and those identified above, we conclude Appellants’ specification would not have enabled any person skilled in the relevant art to use the full scope of their claimed invention. The breadth of Appellants’ enablement is not commensurate in scope with their claims, i.e., methods for treating any “disease mediated by raf kinase” (claim 15), or alternatively, any “solid cancer, melanoma or adenoma” (not just those mediated by raf kinase) (claim 26), with all the compounds of their claimed genus.

Contrary to Appellants’ position, their specification provides scant guidance on how to practice method claims 15 and 26. In fact, the guidance is limited to (1) an *in vitro* cell proliferation assay showing inhibition of two

colon cancer cell lines; and (2) summary instructions relating to an *in vivo* assay in mice that “can be performed” to determine inhibition of a human colon adenocarcinoma cell line. *See* Spec. at 34-35. Given the broad scope of their method claims, these teachings do not provide the “quid” required to receive a patent of the scope Appellants seek.

Appellants rely heavily on the “state of the art.” However, the cited references does not cure the deficiencies of their specification. Considered separately or together, these references invite further research into the treatment of cancer through inhibition of raf kinase. Their invitations are reflected in statements, such as “expected to have antitumor activity in at least a proportion of human tumors” (WO ‘103), “may be of considerable value as antineoplastic agents” (Monia), and “would be potentially useful” (Fridman). Cecil confirms this conclusion. *See, e.g.*, CECIL 1004 (“[C]linical and laboratory observations have provided a reasonable framework” but this “framework must be used with caution . . . because it is certain that the intrinsic factors that control tumor growth and propagation are far more complex, episodic, and heterogeneous than we know, even with a single tumor mass.”).

Thus, contrary to Appellants’ position, the state of the art does not provide enablement for Appellants’ “single therapeutic approach” for the treatment of all diseases “mediated by raf kinase” or for treatment of all solid cancer, melanomas and adenomas, whether or not mediated by raf kinase.

Like the Examiner, our application of the *Wands* factors to the facts of this case leads us to conclude: “In view of the breadth of the claim[s], the chemical nature of the invention, the unpredictability of ligand-receptor



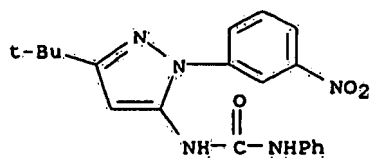
interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.” Answer 6. Undue experimentation would be necessary to use all the generic compounds recited in claim 15 to treat all diseases mediated by raf kinase; likewise undue experimentation would be required to treat all solid tumors, melanomas and adenomas with the large genus of compounds recited in claim 26. *See id.*

35 U.S.C. § 103(a)

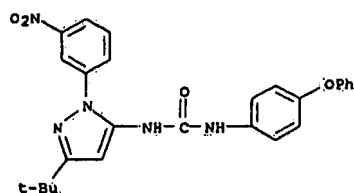
Based on our findings elaborated above and those of the Examiner, we conclude it would have been obvious to the skilled artisan to substitute a phenoxy group on the terminal phenyl of Regan’s Example No. 34, thereby obtaining a compound expressly recited in Appellants’ claim 40.

Motivation for such a combination is found in Regan’s teachings regarding the utility of his disclosed genus—a genus that embraces Appellants’ genus and thus embraces Appellants’ claimed compound, N-(1-(3-nitrophenyl)-3-tert-butyl-5-pyrazolyl)-N’-(4-phenoxyphenyl)urea.

Regan discloses a number of species, including



This compound differs from Appellants’ N-(1-(3-nitrophenyl)-3-tert-butyl-5-pyrazolyl)-N’-(4-phenoxyphenyl)urea by a singly substitution, i.e., Regan’s phenyl (Ph) is substituted with phenoxy (OPh):



Claim 40 (third recited compound).

Regan teaches the equivalency of unsubstituted phenyl and phenyl substituted with phenoxy. Thus, a single substitution in Regan's Example 34 would have resulted in at least one of Appellants' claimed compounds.

One skilled in the relevant art would have reasonably expected that Appellants' N-(1-(3-nitrophenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-phenoxyphenyl)urea, a compound falling within Regan's "ultimately preferred" genus, would be useful as a therapeutic agent and thus would have been motivated to make the substitution. Thus, the invention of Appellants' claim 40 would have been prima facie obvious to one of ordinary skill in the art at the time Appellants' invention was made.

Appellants have not rebutted the Examiner's case of prima facie obviousness with any evidence that their claimed compounds would have unexpected results compared to those disclosed by Regan.

## CONCLUSION

In summary, we affirm the § 112, ¶ 1, rejection of claims 15 and 26 and the § 103(a) rejection of claim 40. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the § 112 rejection of claims 16, 18-23, 27-29, and 38 and the § 103(a) rejection of claims 1, 2, 4-6, 9-10, 15-16, 18-24, 26-31, and 38 (all the remaining claims on appeal), as they were not argued separately.

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No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

dm

GREEN, Administrative Patent Judge, concurring in the result.

I agree with the majority that the rejection of claims 1, 2, 4-6, 9, 10, 15, 16, 18-24, 26-31, 38 and 40, all of the claims on appeal (Br. 2), under 35 U.S.C. § 103(a) as being rendered obvious by the '763 patent to Regan should be affirmed. I do not however, agree with the majority's analysis or conclusion as to the rejection of claims 15, 16 and 18-23 under 35 U.S.C. § 112, for lack of enablement, and would reverse this rejection.

“When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.” *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). “[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In addition, the specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

“[E]nablement requires that the specification teach those in the art to make and use the invention without ‘undue experimentation.’ . . . That *some* experimentation may be required is not fatal; the issue is whether the amount

of experimentation required is ‘undue.’” *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). What is considered undue is relative – it varies from one field to another. *See, e.g., In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1403-04 (factors relating to undue experimentation include quantity of experimentation necessary, nature of the invention, and relative skill of those in the art). “Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field become useful is well before it is ready to be administered to humans.” *In re Brana*, 51 F.3d 1560, 1568, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). (While the *Brana* court referred to “usefulness”, the rejection on appeal was for nonenablement. *See id.* at 1564, 34 USPQ2d at 1439.)

Claim 15, reproduced in the appendix, is drawn to “[a] method for the treatment of disease mediated by raf kinase, comprising administering an effective amount of a compound [of defined formula] or a pharmaceutically acceptable salt thereof to a host in need thereof.”

In the rejection, the Examiner asserts that “the instant claims cover ‘diseases’ that are known to exist and those that may be discovered in the future, for which there is no enablement provided” (Answer 4). The Examiner also cites Cecil to support the assertion that there is no “silver bullet” in cancer therapy (Answer 4), but Cecil is drawn to cancer generally, and not to those cancers mediated by raf kinase. The Examiner also goes through the *Wands* factors, (Answer 4-6). The Examiner asserts that the art is unpredictable, as “[p]harmacological activity in general is a very unpredictable area.” (*Id.* 5) The Examiner also notes with respect to the

amount of guidance and the presence or absence of working examples that “[t]he specification provides assays . . .to test the compounds *in vitro* and discloses that the compounds exhibit raf kinase inhibitory properties. However, no *in vivo* test procedures or data provided for the compounds commensurate in scope of the claims and there is no disclosure regarding how the *in vitro* results correlate to *in vivo* tests. *In vivo* test procedures are provided for the cancers of the colon in mice . . ., however, there is no demonstrated correlation that the tests and results apply to all of the disorders embraced by the instant claims.” (*Id.*).

The Majority, in agreement with the rejection, found that the Specification discloses an *in vitro* raf kinase assay using 32 compounds of the invention, wherein IC<sub>50</sub>s of between 10 nM and 10μM were found. FF 5. The Majority also found that while an *in vitro* assay using colon cancer cells is disclosed by the Specification, as well as *in vivo* assays using a mouse model, FF 6-7, the Specification did not disclose any art-recognized assays or tests that would be predictive of success for the pharmaceutical use of claim 15. FF 8-10.

Appellants rely on Monia, Kolch, Daum and Fridman as representative of the state of the art at the time of invention (Br. 3), and also cite WO 97/36587 and WO 98/22103 as support for the proposition that “the state of the art was not limiting with respect to the types of cancerous cell growth where raf plays a role” (*id.* at 5). The Majority, however, found that the cited references merely invite further research into the treatment of cancer through raf kinase, and thus do not provide enabling support for a claim drawn to a treatment of a disease mediated by raf kinase. FF 11-21.

Daum is a review article, which teaches that raf kinases are involved in a cascade of protein kinases that “mediates transformation by most oncogenes.” Daum, Abstract. The reference notes that raf has been demonstrated to be critical for the induced growth of NIH3T3 fibroblasts, as well as for haemopoietic cell lines and primary bone-marrow cultures through the use of expression of dominant negative mutants, elimination of the protein using antisense RNA, and microinjection of inhibitory antibodies. *Id.* at 478, paragraph bridging the first and second columns. The reference teaches further that “[r]af kinases have been established as critical gatekeepers in growth factor signal transduction and oncogenic transformation.” *Id.* at 479, second column.

Fridman teaches that “a highly specific anti-Ras chemical drug . . . [that] can be delivered efficiently into the cytoplasm . . . would be potentially useful; for treatments of Ras-associated cancers, which represent about 30% of total human carcinomas, notably more than 90% of pancreas carcinomas and 50% of colon carcinomas.” Fridman at 30108.

The majority dismisses the teachings of Daum and Fridman by finding that “[n]either Daum nor Fridman studied the treatment of any type of cancer with a ‘chemical drug,’ such as those claimed by Appellants, or even suggested a possible structure for such a drug.” FF 14. Daum and Fridman, however, demonstrate that it was known in the prior art that inhibition of raf would be expected to inhibit raf-mediated tumor growth.

Kolch teaches that raf is “an attractive target for the design of novel antiproliferative agents . . . .” Kolch at 428, second column.

Monia teaches that “[s]ubstantial evidence exists supporting a direct role for *raf* kinases in the development and maintenance of certain human malignancies.” Monia, Abstract. Monia teaches the use of an antisense oligonucleotide targeted against *raf*, finding that “treatment resulted in potent antiproliferative effects in cell culture and potent antitumor effects *in vivo* against a variety of tumor types . . . .” *Id.*

The Majority fails to consider the above references in their entirety and ignores their more favorable teachings, instead finding that the cited references merely invite further research into the treatment of cancer through *raf* kinase, and thus do not provide enabling support for a claim drawn to a treatment of a disease mediated by *raf* kinase. FF 17-18.

As to WO ’103 and WO ’587, the Majority finds that the discussions in the background sections “set the stage for further research rather than providing enabling disclosure commensurate in scope with Appellants’ method claims.” FF 21. Again, the Majority fails to consider the teachings of these references in the context of the totality of the evidence.

WO ’103 discloses compounds that are inhibitors of *raf* kinase, and cites numerous references to support that inhibition of *raf* will result in anti-tumor activity. WO ’103 at 1-2. The reference states that, “[t]aken together, these findings indicate that *raf* is both a direct and major effector of *ras* function and as such inhibition of the kinase activity of *raf* is expected to have antitumour activity in at least a proportion of human tumours.” *Id.* at 2. The reference discloses further that “[r]*af* inhibitors may also be useful in the treatment of diseases other than cancer that may be associated with signal transduction pathways operating through *Ras*, e.g., neuro-



fibromatosis.” *Id.* Thus, contrary to the finding of the majority, who appear to be requiring clinical data for an enabling disclosure, WO ’103, provides evidence that it was known in the prior art that inhibitors of raf would be expected to be effective in the treatment of raf mediated diseases, such as a proportion of human tumors.

WO ’587 relates to a method of treating cancer by using a combination of a compound that has raf antagonist activity and a compound that that has farnesyl transferase inhibiting activity. WO ’587 at 1. The reference teaches further “[a]ntisense constructs which reduce . . . Raf activity, inhibit the growth of oncogene-transformed rodent fibroblasts in soft agar . . . . Since inhibition of growth in soft agar is highly predictive of tumor responsiveness in whole animals, these studies suggest that the antagonism of Raf is an effective means by which to treat cancers in which Raf plays a role.” *Id.* According to WO ’587, “[e]xamples of cancers where Raf is implicated through overexpression include cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung. More particularly, such examples include histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers. Additional examples include cancers in which overexpression or activation of raf-activating oncogenes . . . is observed. More particularly, such cancers include pancreatic and breast carcinoma.” *Id.*

Thus, the Majority and the examiner have focused on the unpredictability of pharmaceutical inventions in general, as well as the amount of experimentation that may be required to practice the invention of claim 15, appearing to require clinical data before enablement will be found. Under the standard being applied by the Majority, it would seem that very

few disclosures for pharmaceutical inventions would meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

The Examiner and the Majority have not taken into account such other relevant factors as relative skill in the art and the relevant prior art, set forth above. As noted in *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996):

In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim. *See, e.g., In re Goodman*, 11 F.3d 1046, 1050-52, 29 USPQ2d 2010, 2013-15 (Fed. Cir. 1993); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991); *In re Vaeck*, 947 F.2d at 496, 20 USPQ2d at 1445. Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation “must not be unduly extensive.” *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the

specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

*Ex parte Jackson*, 217 USPQ 804, 807 (1982).

In this case, Appellants have synthesized 32 compounds that fall within the claimed genus of compounds, and demonstrated that they are inhibitors of raf kinase. In addition, the prior art demonstrates that the involvement of raf in certain tumor types is well known in the prior art, and further teaches that inhibition of raf kinase results in inhibition of tumor growth in a proportion of human tumors. Neither the Examiner nor the Majority present specific evidence that, in my determination, refutes the presumption that the specification enables the skilled artisan to practice the claimed invention. Thus, the Office has not met its burden of demonstrating, by a preponderance of the evidence, that it would require an undue amount of experimentation to practice the method of claim 15, and I would reverse the rejection as to that claim and the claims dependent thereon.

Further, I also take issue with the Examiner's statement that "the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided," which the Majority quoted in framing the enablement issue. The legal question of enablement involves an assessment of whether a patent disclosure would have enabled one of skill in the art at the time the application was filed to make and use the claimed invention without undue experimentation.

*Hybritech Inc.*, 802 F.2d at 1384, 231 USPQ at 94. Thus, there is no

requirement that the specification enable the treatment of diseases that may be discovered in the future in order to provide an enabling disclosure.

Moreover, the Majority appears to be interpreting “[a] method for the treatment of disease mediated by raf kinase” as requiring treatment of *any and all* diseases mediated by raf kinase. That however, is not the standard for enablement under 35 U.S.C. § 112, first paragraph.

A claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. § 112, first paragraph. *See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976) (“Without undue experimentation . . . the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them.”), *In re Cook*, 439 F.2d 730, 732, 169 USPQ 298, 300 (CCPA 1971) (“We agree that appellants’ claims are not too broad “to the point of invalidity” just because they read on even a large number of inoperative embodiments, since it seems to be conceded that a person skilled in the relevant art could determine which conceived but not-yet-fabricated embodiments would be inoperative with expenditure of no more effort than is normally required of a lens designer checking out a proposed set of parameters.”), *Capon v. Eshhar*, 418 F.3d 1349, 1359, 76 USPQ2d 1078, 1085-86 (Fed. Cir. 2005) (“it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention.”).

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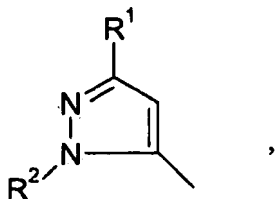
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## APPENDIX

15. A method for the treatment of disease mediated by raf kinase, comprising administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof to a host in need thereof:



wherein A is



wherein  $R^1$  is selected from the group consisting of  $C_3$ - $C_{10}$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl, up to per-halosubstituted  $C_1$ - $C_{10}$  alkyl or up to per-halosubstituted  $C_3$ - $C_{10}$  cycloalkyl;

B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, substituted by  $-M-L^1$  and optionally substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and  $X_n$ ,

wherein n is 0-2 and each X is independently selected from the group consisting of  $-\text{CN}$ ,  $\text{CO}_2\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{5'}$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{NO}_2$ ,  $-\text{OR}^5$ ,  $-\text{SR}^5$ ,

$-\text{NR}^5\text{R}^{5'}$ ,  $-\text{NR}^5\text{C}(\text{O})\text{OR}^{5'}$ ,  $-\text{NR}^5\text{C}(\text{O})\text{R}^{5'}$ ,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_2\text{-C}_{10}$  alkenyl,  $\text{C}_1\text{-C}_{10}$  alkoxy,  $\text{C}_3\text{-C}_{10}$  cycloalkyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_7\text{-C}_{24}$  alkaryl,  $\text{C}_3\text{-C}_{13}$  heteroaryl,  $\text{C}_4\text{-C}_{23}$  alkheteroaryl, substituted  $\text{C}_1\text{-C}_{10}$  alkyl, substituted  $\text{C}_2\text{-C}_{10}$  alkenyl, substituted  $\text{C}_1\text{-C}_{10}$  -alkoxy, substituted  $\text{C}_3\text{-C}_{10}$  cycloalkyl, up to per-halosubstituted  $\text{C}_6\text{-C}_{14}$  aryl, up to per-halosubstituted  $\text{C}_3\text{-C}_{13}$  heteroaryl, substituted  $\text{C}_4\text{-C}_{23}$  alkheteroaryl and  $\text{M-L}^1$ ;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of  $-\text{CN}$ ,  $\text{CO}_2\text{R}^5$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{5'}$ ,  $-\text{OR}^5$ ,  $-\text{SR}^5$ ,  $-\text{NR}^5\text{R}^{5'}$ ,  $-\text{NO}_2$ ,  $-\text{NR}^5\text{C}(\text{O})\text{R}^{5'}$ ,  $-\text{NR}^5\text{C}(\text{O})\text{OR}^{5'}$  and halogen up to per-halosubstitution;

wherein  $\text{R}^5$  and  $\text{R}^{5'}$  are independently selected from  $\text{H}$ ,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_2\text{-C}_{10}$  alkenyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_3\text{-C}_{13}$  heteroaryl,  $\text{C}_7\text{-C}_{24}$  alkaryl,  $\text{C}_4\text{-C}_{23}$  alkheteroaryl, up to per-halosubstituted  $\text{C}_1\text{-C}_{10}$  alkyl, up to per-halosubstituted  $\text{C}_2\text{-C}_{10}$  alkenyl, up to per-halosubstituted  $\text{C}_3\text{-C}_{10}$  cycloalkyl, up to per-halosubstituted  $\text{C}_6\text{-C}_{14}$  aryl and up to per-halosubstituted  $\text{C}_3\text{-C}_{13}$  heteroaryl,

wherein M is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{N}(\text{R}^5)-$ ,  $-(\text{CH}_2)_m-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{CH}(\text{OH})-$ ,  $-(\text{CH}_2)_m\text{O}-$ ,  $-(\text{CH}_2)_m\text{S}-$ ,  $-(\text{CH}_2)_m\text{N}(\text{R}^5)-$ ,  $-\text{O}(\text{CH}_2)_m-$ ,  $-\text{CHX}^a-$ ,  $-\text{CHX}^a_2-$ ,  $-\text{S}-(\text{CH}_2)_m-$  or  $-\text{N}(\text{R}^5)(\text{CH}_2)_m-$ ,  $m = 1-3$ , and  $\text{X}^a$  is halogen; and

$\text{L}^1$  is a 5- or 6-member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur atoms which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by  $\text{Z}_{n1}$ , wherein  $n1$  is 0 to 3 and each Z is independently  $-\text{CN}$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $\text{CO}_2\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{5'}$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{NO}_2$ ,  $-\text{OR}^5$ ,  $-\text{SR}^5$ ,  $-\text{NR}^5\text{R}^{5'}$ ,  $-\text{NR}^5\text{C}(\text{O})\text{OR}^{5'}$ ,  $-\text{NR}^5\text{C}(\text{O})\text{R}^{5'}$ ,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_3\text{-C}_{13}$  heteroaryl,  $\text{C}_7\text{-C}_{24}$  alkaryl,  $\text{C}_4\text{-C}_{23}$  alkheteroaryl,

substituted C<sub>1</sub>-C<sub>10</sub> alkyl, substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, substituted C<sub>7</sub>-C<sub>24</sub> alkaryl or substituted C<sub>4</sub>-C<sub>23</sub> alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of -CN, CO<sub>2</sub>R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>5'</sup>, -OR<sup>5</sup>, -SR<sup>5</sup>, -NO<sub>2</sub>, -NR<sup>5</sup>R<sup>5'</sup>, -NR<sup>5</sup>C(O)R<sup>5'</sup> and -NR<sup>5</sup>C(O)OR<sup>5'</sup>, and

wherein R<sup>2</sup> is C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>3</sub>-C<sub>14</sub> heteroaryl, substituted C<sub>6</sub>-C<sub>14</sub> aryl or substituted C<sub>3</sub>-C<sub>14</sub> heteroaryl,

wherein if R<sup>2</sup> is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V<sub>n</sub>,

wherein n = 0-3 and each V is independently selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>5'</sup>, -OR<sup>5</sup>, -SR<sup>5</sup>, -NR<sup>5</sup>R<sup>5'</sup>, -OC(O)NR<sup>5</sup>R<sup>5'</sup>, -NR<sup>5</sup>C(O)OR<sup>5'</sup>, -NR<sup>5</sup>C(O)OR<sup>5'</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SOR<sup>5</sup>, -NR<sup>5</sup>C(O)R<sup>5'</sup>, -NO<sub>2</sub>, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>3</sub>-C<sub>13</sub> heteroaryl, C<sub>7</sub>-C<sub>24</sub> alkaryl, C<sub>4</sub>-C<sub>24</sub> alkheteroaryl, substituted C<sub>1</sub>-C<sub>10</sub> alkyl, substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, substituted C<sub>6</sub>-C<sub>14</sub> aryl, substituted C<sub>3</sub>-C<sub>13</sub> heteroaryl, substituted C<sub>7</sub>-C<sub>24</sub> alkaryl, substituted C<sub>4</sub>-C<sub>24</sub> alkheteroaryl,

where V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, -CO<sub>2</sub>R<sup>5</sup>, -C(O)R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>5'</sup>, -NR<sup>5</sup>R<sup>5'</sup>, -OR<sup>5</sup>, -SR<sup>5</sup>, -NR<sup>5</sup>C(O)R<sup>5'</sup>, -NR<sup>5</sup>C(O)OR<sup>5'</sup> and -NO<sub>2</sub>,

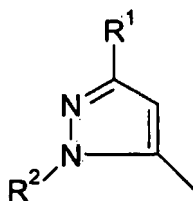
wherein R<sup>5</sup> and R<sup>5'</sup> are each independently as defined above.



26. A method for treating a solid cancer, melanoma or adenoma, comprising administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof to a host in need thereof:



wherein A is



wherein R<sup>1</sup> is selected from the group consisting of C<sub>3</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, up to per-halosubstituted C<sub>1</sub>-C<sub>10</sub> alkyl and up to per-halosubstituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl;

B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, substituted by -M-L<sup>1</sup> and optionally substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X<sub>n</sub>,

wherein n is 0-2 and each X is independently selected from the group consisting of -CN, CO<sub>2</sub>R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>5'</sup>, -C(O)R<sup>5</sup>, -NO<sub>2</sub>, -OR<sup>5</sup>, -SR<sup>5</sup>, -NR<sup>5</sup>R<sup>5'</sup>, -NR<sup>5</sup>C(O)OR<sup>5'</sup>, -NR<sup>5</sup>C(O)R<sup>5'</sup>, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>7</sub>-C<sub>24</sub> alkaryl, C<sub>3</sub>-C<sub>13</sub> heteroaryl, C<sub>4</sub>-C<sub>23</sub> alkheteroaryl, substituted C<sub>1</sub>-C<sub>10</sub> alkyl, substituted C<sub>2</sub>-C<sub>10</sub> alkenyl, substituted C<sub>1</sub>-C<sub>10</sub> -alkoxy, substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, up to per-

halosubstituted C<sub>6</sub>-C<sub>14</sub> aryl, up to per-halosubstituted C<sub>3</sub>-C<sub>13</sub> heteroaryl substituted C<sub>4</sub>-C<sub>23</sub> alkheteroaryl and M-L<sup>1</sup>;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, CO<sub>2</sub>R<sup>5</sup>, -C(O)R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>5'</sup>, -OR<sup>5</sup>, -SR<sup>5</sup>, -NR<sup>5</sup>R<sup>5'</sup>, -NO<sub>2</sub>, -NR<sup>5</sup>C(O)R<sup>5'</sup>, -NR<sup>5</sup>C(O)OR<sup>5'</sup> and halogen up to per-halosubstitution;

wherein R<sup>5</sup> and R<sup>5'</sup> are independently selected from H, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>3</sub>-C<sub>13</sub> heteroaryl, C<sub>7</sub>-C<sub>24</sub> alkaryl, C<sub>4</sub>-C<sub>23</sub> alkheteroaryl, up to per-halosubstituted C<sub>1</sub>-C<sub>10</sub> alkyl, up to per-halosubstituted C<sub>2</sub>-C<sub>10</sub> alkenyl, up to per-halosubstituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, up to per-halosubstituted C<sub>6</sub>-C<sub>14</sub> aryl and up to per-halosubstituted C<sub>3</sub>-C<sub>13</sub> heteroaryl,

wherein M is -O-, -S-, -N(R<sup>5</sup>)-, -(CH<sub>2</sub>)<sub>m</sub>-, -C(O)-, -CH(OH)-, -(CH<sub>2</sub>)<sub>m</sub>O-, -(CH<sub>2</sub>)<sub>m</sub>S-, -(CH<sub>2</sub>)<sub>m</sub>N(R<sup>5</sup>)-, -O(CH<sub>2</sub>)<sub>m</sub>-, -CHX<sup>a</sup>-, -CHX<sup>a</sup><sub>2</sub>-, -S-(CH<sub>2</sub>)<sub>m</sub>- or -N(R<sup>5</sup>)(CH<sub>2</sub>)<sub>m</sub>-, m = 1-3, and X<sup>a</sup> is halogen; and

L<sup>1</sup> is a 5- or 6-member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur atoms which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z<sub>n1</sub>, wherein n1 is 0 to 3 and each Z is independently -CN, -C(O)R<sup>5</sup>, CO<sub>2</sub>R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>5'</sup>, -C(O)R<sup>5</sup>, -NO<sub>2</sub>, -OR<sup>5</sup>, -SR<sup>5</sup>, -NR<sup>5</sup>R<sup>5'</sup>, -NR<sup>5</sup>C(O)OR<sup>5'</sup>, -NR<sup>5</sup>C(O)R<sup>5'</sup>, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>3</sub>-C<sub>13</sub> heteroaryl, C<sub>7</sub>-C<sub>24</sub> alkaryl, C<sub>4</sub>-C<sub>23</sub> alkheteroaryl, substituted C<sub>1</sub>-C<sub>10</sub> alkyl, substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl, substituted C<sub>7</sub>-C<sub>24</sub> alkaryl or substituted C<sub>4</sub>-C<sub>23</sub> alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of -CN,

$\text{CO}_2\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{5'}$ ,  $-\text{OR}^5$ ,  $-\text{SR}^5$ ,  $-\text{NO}_2$ ,  $-\text{NR}^5\text{R}^{5'}$ ,  $-\text{NR}^5\text{C}(\text{O})\text{R}^{5'}$  and  $-\text{NR}^5\text{C}(\text{O})\text{OR}^{5'}$ , and

wherein  $\text{R}^2$  is  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_3\text{-C}_{14}$  heteroaryl, substituted  $\text{C}_6\text{-C}_{14}$  aryl or substituted  $\text{C}_3\text{-C}_{14}$  heteroaryl,

wherein if  $\text{R}^2$  is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and  $\text{V}_n$ ,

wherein  $n = 0\text{-}3$  and each  $\text{V}$  is independently selected from the group consisting of  $-\text{CN}$ ,  $-\text{CO}_2\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{5'}$ ,  $-\text{OR}^5$ ,  $-\text{SR}^5$ ,  $-\text{NR}^5\text{R}^{5'}$ ,  $-\text{OC}(\text{O})\text{NR}^5\text{R}^{5'}$ ,  $-\text{NR}^5\text{C}(\text{O})\text{OR}^{5'}$ ,  $-\text{NR}^5\text{C}(\text{O})\text{OR}^{5'}$ ,  $-\text{SO}_2\text{R}^5$ ,  $-\text{SOR}^5$ ,  $-\text{NR}^5\text{C}(\text{O})\text{R}^{5'}$ ,  $-\text{NO}_2$ ,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_3\text{-C}_{13}$  heteroaryl,  $\text{C}_7\text{-C}_{24}$  alkaryl,  $\text{C}_4\text{-C}_{24}$  alkheteroaryl, substituted  $\text{C}_1\text{-C}_{10}$  alkyl, substituted  $\text{C}_3\text{-C}_{10}$  cycloalkyl, substituted  $\text{C}_6\text{-C}_{14}$  aryl, substituted  $\text{C}_3\text{-C}_{13}$  heteroaryl, substituted  $\text{C}_7\text{-C}_{24}$  alkaryl, substituted  $\text{C}_4\text{-C}_{24}$  alkheteroaryl,

where  $\text{V}$  is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution,  $-\text{CN}$ ,  $-\text{CO}_2\text{R}^5$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{5'}$ ,  $-\text{NR}^5\text{R}^{5'}$ ,  $-\text{OR}^5$ ,  $-\text{SR}^5$ ,  $-\text{NR}^5\text{C}(\text{O})\text{R}^{5'}$ ,  $-\text{NR}^5\text{C}(\text{O})\text{OR}^{5'}$  and  $-\text{NO}_2$ ,

wherein  $\text{R}^5$  and  $\text{R}^{5'}$  are each independently as defined above.

40. A compound which is

$\text{N}-(1-(3\text{-aminophenyl})-3\text{-tert-butyl-5-pyrazolyl})-\text{N}'-(4\text{-phenoxyphenyl})$  urea;

$\text{N}-(1-(3\text{-actamidophenyl})-3\text{-tert-butyl-5-pyrazolyl})-\text{N}'-(4\text{-phenoxyphenyl})$  urea;

$\text{N}-(1-(3\text{-nitrophenyl})-3\text{-tert-butyl-5-pyrazolyl})-\text{N}'-(4\text{-phenoxyphenyl})$  urea;

N-(1-(phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(4 pyridinyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(2, 5 dichloro phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(4-fluoro phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(2-methyl phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(3 fluoro phenyl)-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(4-methylsulfoxy phenyl)-3-tert-butyl- 5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(4-nitro phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(3-methoxy phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(3-amino phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(3-nitro phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl methyl)phenyl) urea;

N-(1-(3-amino phenyl) -3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinyl thio) phenyl) urea.